IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: Haim AVIV et al.	Confirmation No.: 6729
Application No.: 10/644,687	Group Art Unit: 1626
Filing Date: August 19, 2003	Examiner: Taofiq A. Solola
For: HIGH ENANTIOMERIC PURITY DEXANABINOL FOR PHARMACEUTICAL COMPOSITIONS	Attorney Docket No.: 87754-7500

APPEAL BRIEF

Mail Stop Appeal Brief-Patents
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

Appellants appeal to the Board of Patent Appeals and Interferences (the "Board") from the decision of the Examiner mailed December 5, 2005 rejecting claims 1-6 and 8-24. The statutory small-entity fee of $250.00 was submitted previously on March 30, 2006 with the Pre-Appeal Brief Request for Review.

1. REAL PARTY IN INTEREST

The real party in interest is Pharmos Corporation ("Pharmos"), having a business address of 99 Wood Avenue South, Iselin, New Jersey 08830, the assignee of the entire right, title, and interest in the invention described and claimed in the above-identified patent application. The invention was assigned by Haim Aviv, Raphael Bar, Michael Schickler, and Shimon Amselem to Pharmos. The assignment was recorded on September 23, 2003 at reel 014600, frame 0360.

2. RELATED APPEALS AND INTERFERENCES

Appellants and its legal representatives are not aware of any appeal or interference that directly affects, will be directly affected by, or will have a bearing on the Board's decision in this appeal.

3. STATUS OF CLAIMS

Claims 1-24 were submitted upon filing of application 10/644,687. In an Office Action dated October 1, 2004, claims 21-24 were rejected as not enabled; claims 1-10, 15, 16, and 18-24 were rejected as being anticipated by U.S. Patent No. 5,284,867 to Kloog et al. ("Kloog"); and claims 1-24 were rejected as being unpatentable over Kloog. A response was filed on March 9, 2005, including the Declaration of Raphael Mechoulam under 37 C.F.R. § 1.132 in support of Appellants' position. Claim 7 was cancelled and claims 4, 8-11, and 21 were amended.

In a Final Office Action dated April 22, 2005, claims 1-10, 15, 16, and 18-24 were rejected as anticipated by Kloog, and claims 1-24 were rejected as being unpatentable over Kloog. An interview with the Examiner was held on June 28, 2005. A Response to the Final Office Action was filed June 30, 2005. None of the pending claims were amended.

An Advisory Action mailed August 3, 2005, indicated that the Response to the Final Office Action did not place the application in condition for allowance because a side-by-side study was not submitted. A Response to the Advisory Action was filed on September 14, 2005, including the Declaration of Avihai Yacovan. None of the pending claims were amended. A Request for Continued Examination was filed on October 24, 2005.

A Final Office Action was mailed on December 5, 2005, which rejected claims 1-10, 15, 16, and 18-24 as anticipated by Kloog, and claims 1-6 and 8-24 as unpatentable over Kloog. A Response to the Final Office Action dated March 6, 2006, including the Declaration of Raphael Bar was submitted. None of the pending claims were amended.

An Advisory Action mailed on March 16, 2006 indicated that the March 6, 2006 Response did not place the application in condition for allowance because the affidavit failed to overcome the rejections.

A Pre-Appeal Brief Request for Review was filed on March 30, 2006. A Notice of Panel Decision from Pre-Appeal Brief Review was mailed on April 13, 2006, indicating that the application remains under appeal because there is at least one actual issue for appeal.

Claims 1-6 and 8-24 have been twice rejected in their present form.

Claims 1-6 and 8-24 are presented in Appendix A.

4. STATUS OF AMENDMENTS

Claim 7 has been cancelled, and claims 4, 8-11, and 21 have been amended.

In an amendment filed March 9, 2005, claim 7 was cancelled and claims 4, 8-11, and 21 were amended. The Declaration of Raphael Mechoulam under 37 C.F.R. § 1.132 was filed concurrently.

A Response to Final Office Action was filed June 30, 2005, making no amendments.

A Response to Advisory Action was filed on September 14, 2005, including the Declaration of Avihai Yacovan, making no amendments.

A Request for Continued Examination was filed on October 24, 2005.

A Response to Final Office Action was filed March 6, 2006, including the Declaration of Raphael Bar, making no amendments.

A Pre-Appeal Brief Request for Review was filed on March 30, 2006.

5. SUMMARY OF CLAIMED SUBJECT MATTER

The present invention generally relates to enantiomerically pure dexanabinol, pharmaceutical compositions containing the dexanabinol, and methods of treatment by administering the dexanabinol.

Claim 1 defines the dexanabinol as having the (3S,4S) configuration (Specification, page 6, lines 5-10) and being in enantiomeric excess of at least 99.90% over the (3R,4R) enantiomer (Specification, page 6, lines 10-11), or a pharmaceutically acceptable salt, ester, or solvate thereof (Specification, page 6, line 11).

Claim 4 defines a pharmaceutical composition that includes as its active ingredient dexanabinol having the (3S, 4S) configuration (Specification, page 6, lines 18-19) and being in enantiomeric excess of at least 99.90% over the (3R, 4R) enantiomer, or a pharmaceutically acceptable salt, ester, or solvate thereof (Specification, page 6, lines 20-21). The composition also includes a pharmaceutically acceptable diluent or carrier (Specification, page 6, line 22-23).

Claim 21 defines a method for treating neurological disorders, chronic degenerative diseases, CNS poisoning, cognitive impairment, inflammatory diseases or disorders, autoimmune diseases or disorders, pain, emesis, glaucoma and wasting syndromes,

(Specification, page 7, lines 8-12) by administering a therapeutically effective amount of a pharmaceutical composition that includes as an active ingredient the dexanabinol of claim 1 (Specification, page 7, lines 12-14).

The present invention provides unexpected advantages conferred by the high degree of enantiomeric purity of the claimed compound. It is known that the psychotropic activity of cannabinoids resides in the natural (3R,4R) enantiomers, while the opposite synthetic (3S,4S) enantiomers are free of these undesirable effects. Thus, in order to exploit the therapeutic value of cannabinoids, the highly undesirable psychoactive effects would have to be "neutralized," for instance by preparation and selection of synthetic non-psychotropic enantiomers.

6. GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

Claims 1-10, 15, 16, and 18-24 are rejected under 35 U.S.C. § 102(b) as anticipated by Kloog. Claims 1-6 and 8-24 were rejected under 35 U.S.C. § 103(a) as being obvious over Kloog.

7. ARGUMENT

The Examiner's rejections of the pending claims are in error because the enantiomeric purity of the compounds of the invention are neither taught nor suggested in the disclosure in Kloog, and the present claims are therefore not anticipated or rendered obvious by Kloog. For the reasons below, Appellants respectfully request that the Examiner's anticipation and obviousness rejections be reversed, and that claims 1-6 and 8-24 be allowed.

A. <u>The Present Invention Is Not Anticipated by Kloog</u>

Kloog discloses the compound HU-211 (dexanabinol), *i.e.* the (3S,4S) enantiomer of 1,1-dimethylheptyl-(3S,4S)-7-hydroxy-Δ^6-tetrahydrocannabinol, which is "essentially free" of the (3R,4R) enantiomer (HU-210).[1] However, Kloog's HU-211 and the presently claimed high purity HU-211 are significantly different compounds with different properties, which are attributable to the differences in enantiomeric purity.

[1] Col. 4, lines 13-16.

The Examiner notes that the difference between the claimed invention and Kloog is that the claims recite a compound having (3S, 4S) enantiomeric excess of at least 99.90% over the (3R, 4R) enantiomer, while Kloog teaches that the compound is essentially free of the (3R, 4R) enantiomer.[2] The Examiner further states that the difference between 99.4% enantiomeric excess in the Kloog sample and 99.9% enantiomeric excess in the presently claimed compound is within experimental error and/or design.[3] Appellants traverse these statements and assumptions.

First of all, the Examiner admits that the present claims recite a value that is different from that disclosed in Kloog. For this reason alone, there should be no rejection based on anticipation. Furthermore, the difference between the claimed value and the value of an "essentially free" enantiomer according to Kloog is much more than a difference in experimental error, as Kloog simply cannot obtain the presently claimed purity due to the method of making that he discloses.

To demonstrate that Kloog does not disclose the claimed compound, Appellants submitted the results of a study comparing the properties of Kloog's HU-211 and the claimed HU-211.[4] Appellants note that Kloog does not teach the synthesis of HU-211, but only describes that the acetylation of HU-211 results in a mixture of HU-211, HU-247, compound A, and compound B.[5] Kloog also teaches that HU-211 can be recovered as the starting material by reducing compounds A and B with $LiAlH_4$.[6]

As there is no synthetic route disclosed in Kloog, it is understood that Kloog's HU-211 was prepared by Professor Raphael Mechoulam, a co-inventor in Kloog.[7] Thus, the compound disclosed in Kloog is a sample that was prepared according to procedures known and used by Mechoulam. In this case, Appellants understand that the compound of Kloog was

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[2] Final Office Action dated December 5, 2005, page 3.

[3] *Id.*

[4] *See* Yacovan Declaration.

[5] Kloog (Col. 6, lines 10-65).

[6] Kloog (Col. 6, lines 66-67).

[7] Bar Declaration, ¶ 6.

prepared according to the original synthetic procedure developed by Mechoulam.[8] U.S. Patent No. 4,876,276 to Mechoulam et al. discloses the laboratory scale synthesis of HU-211.

A sample was prepared according to a slightly modified version of Mechoulam's original synthetic procedure ("Mechoulam sample").[9] Indeed, the Mechoulam sample obtained by the modified procedure either corresponds to the Kloog sample or is even superior to the Kloog sample, such that comparison of a true Kloog sample with the claimed compound ("Ultrapure sample") would have been less favorable to the Kloog sample.[10] Appellants therefore submit that the Mechoulam sample is representative of the closest prior art and is an equivalent or even closer comparison than the Kloog sample.

The Mechoulam sample was tested and found to contain 91.1% HU-211 and 0.26% HU-210, yielding an enantiomeric excess of 99.4%,[11] which is less than the at least 99.90% claimed. These values represent the best values that could have been obtained by Kloog[12] and distinguish the presently claimed compound from that disclosed in Kloog. Thus, the anticipation rejection has been overcome and should be withdrawn.

As noted above, the difference between these two compounds is much more than just the level of purity, as these compounds have significantly different properties. Kloog reports that the inventors discovered that HU-211 at about 25 mg/kg per body weight, administered most likely to mice, induced side effects such as stereotypy, locomotor hyperactivity and tachycardia.[13] In contrast, the compound of the present invention was administered at single doses of 50 mg/kg in rats, 25 mg/kg in rabbits and 50 mg/kg in monkeys, with no observed adverse effects.[14] This establishes that the presently claimed compounds are novel over the Kloog compound.

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[8] *Id.*

[9] *Id.*

[10] *Id.*

[11] *Id.* at ¶ 7 and Yacovan Declaration, ¶ 5.

[12] Yacovan Declaration, ¶ 5.

[13] Col. 5, lines 26-32.

[14] Specification at page 33, lines 26-28.

In addition, three of the four parameters usually tested in the mice tetrad assay were performed on ICR male mice.[15] The animals were administered the Mechoulam or Ultrapure sample intravenously at a dose of 50 mg/kg and at a volume dose of 5 mL/kg.[16] Untreated animals and animals injected with only the vehicle served as controls.[17] Measurements evaluating suppression of spontaneous activity, hypothermia, and catalepsy were taken.[18] The results of the tests are provided in the table below:[19]

Treatment	Rectal Temperature (°C)	Spontaneous Locomotion (No. of Squares)	Catalepsy (Sec)
Untreated (Control)	38.78 ± 0.18	74.51 ± 9.96	0.00 ± 0.00
Ultrapure	38.48 ± 0.12	86.58 ± 13.12	0.00 ± 0.00
Mechoulam	32.96 ± 0.25	4.42 ± 3.13	29.40 ± 8.69

The results show that the Mechoulam sample clearly produces adverse effects, while the Ultrapure sample does not.[20] For example, the Mechoulam sample caused a drastic drop in rectal temperature, almost totally inhibited spontaneous locomotion, and caused significant catalepsy.[21] Thus, it can be inferred from the results that Kloog's HU-211 and the HU-211 claimed are significantly different compounds with different properties.

Consequently, Kloog cannot anticipate the claimed invention because it does not teach or disclose each and every feature in the claims.

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[15] Yacovan Declaration, ¶ 7.

[16] *Id.*

[17] *Id.*

[18] *Id.*

[19] *Id.* at ¶ 8.

[20] *Id.* at ¶ 9.

[21] *Id.*

B. The Present Invention Is Not Obvious in View of Kloog

To establish an obviousness rejection, there must be a showing that the prior art teaches or suggests each and every element of the claimed invention.[22] It is important to note that the 99.90% value is not an absolute purity, but is an enantiomeric excess percentage. Enantiomeric excess is different from purity in general and is derived from the following formula:

percent enantiomeric excess = 100 x ([HU-211] - [HU-210])/([HU-211] + [HU-210])

wherein the concentration of the enantiomers is separately determined by HPLC and expressed as percent by weight.[23] Kloog does not disclose any importance to achieving a 99.90% enantiomeric excess and does not disclose a process for obtaining such excess.

Appellants assert that the difference between the 99.4% and 99.9% is not within experimental error as suggested by the Examiner. As described previously, this distinction results in significantly different biological properties of HU-211.[24] Animals that were administered the Mechoulam sample displayed dramatic hypothermia, catalepsy, and locomotor inhibition.[25] In contrast, animals that were treated with the Ultrapure sample did not exhibit any of these adverse side effects.[26]

The presence of only 0.26% HU-210 (a seemingly small amount) is enough to cause these serious side effects.[27] As Kloog cannot obtain a higher purity than that, his compound cannot inherently achieve the properties of the presently claimed compound. Rather than being some type of optimization of purity of a known compound, the present Appellants instead had to develop a completely different route of synthesis to achieve the level of purity appropriate to avoid such side effects and provide for safe administration of HU-211.[28]

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[22] *In re Royka*, 490 F.2d. 981, 180 USPQ 580 (CCPA 1974).

[23] Specification at page 8, lines 15-21.

[24] Bar Declaration, ¶ 8.

[25] *Id.*

[26] *Id.*

[27] *Id.*

[28] *Id.*

Certainly, these properties could not have been discovered without a process for synthesizing the compound to such high purity levels. The Mechoulam sample that was prepared according to Mechoulam's synthetic route simply does not provide above 98% absolute amount of HU-211 and below 0.05% absolute amount of HU-210, to yield an enantiomeric excess of above 99.90%, and there is nothing in Kloog to teach or motivate one of ordinary skill in the art to obtain this higher purity with its attendant benefits in compound properties.

In addition, while 99.4% and 99.9% appear at first glance to be very close in value, these values refer to calculated enantiomeric excess percentages that do not reflect the original absolute amounts of the individual enantiomers.[29] The content of HU-211 in the Mechoulam sample is 91.1%, while that in the Ultrapure sample is 98.8%. This is a difference of more than 7.5%.[30] The content of HU-210 in the Mechoulam sample at 0.26% is more than 10 times that in the Ultrapure sample.[31] These differences in content are not attributable to experimental variation, and are certainly more than a person of skill in the art would accept from validated analytical methods.[32]

Furthermore, in order to obtain the claimed excess, Appellants, using industrially applicable methods, discovered for the first time a new route of synthesis suitable for preparing large scale quantities of compounds having such properties.[33] Example 1 discloses preparation of high enantiomeric purity dexanabinol on a commercial, intermediate scale. The crystallization performed in the last step of the synthesis of dexanabinol is crucial for the purity of the final product.[34] Specifically, the product of the last step is recrystallized from acetonitrile and then from a 1:1.2 water:ethanol mixture.[35] Example 2 discloses the large scale preparation of dexanabinol of high enantiomeric purity. The pivotal recrystallization step is performed using

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[29] *Id.* at ¶ 9.

[30] *Id.*

[31] *Id.*

[32] *Id.*

[33] *See* Specification, Examples 1 and 2.

[34] Specification at page 20, line 9.

[35] *See* Specification at page 20, lines 5-8.

acetonitrile, which is removed by recrystallization from a 3:5 ethanol:heptane mixture.[36] The advantages of Appellants' new route of synthesis include scale-up ability, improved yield, simplified process, reduced use of toxic chemicals or dangerous reagents, utilization of solvents appropriate for large-scale synthesis, and the adaptation or elimination of certain isolation and purification steps enabling a simplified continuous process.[37] The new route of synthesis results in improved enantiomeric purity and superior enantiomeric excess of clinical grade dexanabinol. And while it is understood that Appellants are not claiming a process, it is respectfully submitted that the prior art cannot obtain the presently claimed compound without some way of obtaining it, and the present process has been found to be the easiest and most expeditious way of doing this. Nothing in Kloog suggests how to obtain the presently claimed level of purity.

Appellants also developed analytical methods accurate and sensitive enough to detect the differences in absolute amounts of HU-210 and HU-211.[38] Past methods could not determine the amount of these enantiomers accurately, especially the small amount of HU-210.[39] Appellants' methods allow detection of HU-210 at a concentration of as low as 0.125 μg/mL.[40] The two linearity plots presented in the Bar Declaration illustrate both the accuracy and sensitivity of these methods.[41] The superiority of these methods demonstrate that the absolute amounts of HU-210 and HU-211 in the Mechoulam and Ultrapure samples are not within experimental error, and consequently, neither are the enantiomeric excess percentages.[42]

Accordingly, because Kloog does not teach the claimed enantiomeric excess, nor does he teach or disclose how to obtain the high purity levels of the presently claimed compounds, he certainly cannot render the present claims obvious. Again, Kloog neither discloses the claimed purity, or how to obtain it, and for these reasons he does not disclose in an obvious manner a way to obtain the desirable properties of the present compounds.

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[36] *See* Specification at page 24, lines 7-14.

[37] *See* Specification at page 15, lines 14-17 and page 24, lines 15-17.

[38] *See* Specification at page 8, lines 22-29 and Bar Declaration, ¶ 10.

[39] Bar Declaration, ¶ 10.

[40] *Id.*

[41] *See* Bar Declaration at page 4.

[42] Bar Declaration, ¶ 10.

8. CONCLUSION

In view of the preceding discussion, Appellants respectfully request that the rejections of claims 1-6 and 8-24 be reversed and that these claims be allowed.

Respectfully submitted,

Date: 5-23-06

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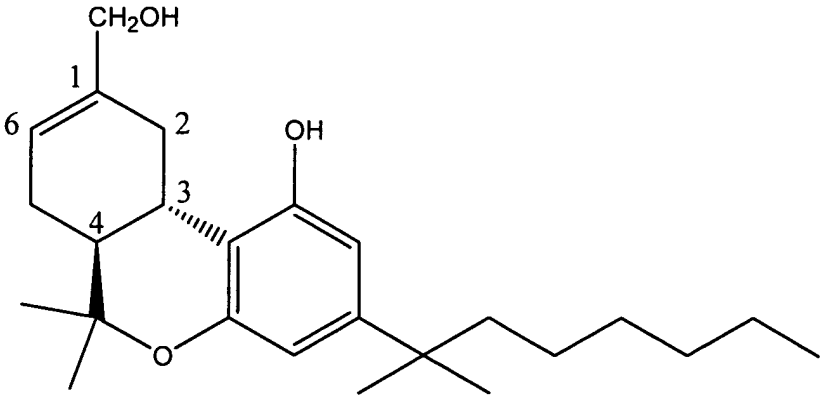
212-294-3311

Appendix A -- Claims Appendix

The claim on appeal are:

1. A compound of formula (I):

Formula I



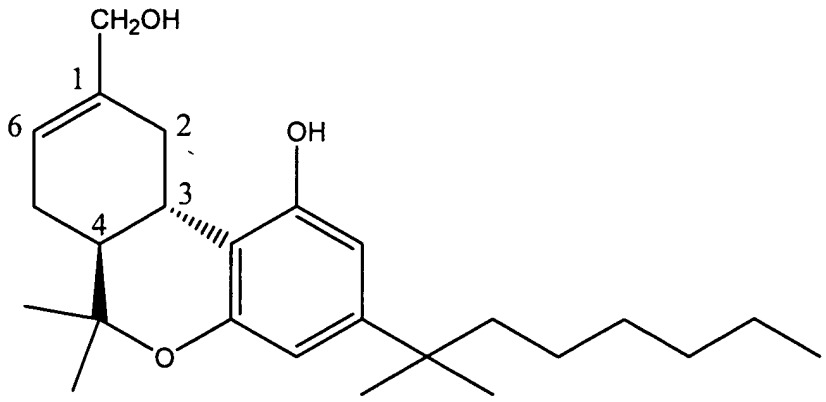
having the (3S,4S) configuration and being in enantiomeric excess of at least 99.90% over the (3R,4R) enantiomer, or a pharmaceutically acceptable salt, ester or solvate of said compound.

2. The compound of claim 1 or a pharmaceutically acceptable salt, ester or solvate of said compound, having the (3S,4S) configuration and being in enantiomeric excess of at least 99.92% over the (3R,4R) enantiomer.

3. The compound of claim 2 or a pharmaceutically acceptable salt, ester or solvate of said compound, having the (3S,4S) configuration and being in enantiomeric excess of at least 99.95% over the (3R,4R) enantiomer.

4. A pharmaceutical composition comprising as an active ingredient dexanabinol, a compound of formula (I):

Formula I



having the (3S,4S) configuration and being in enantiomeric excess of at least 99.90% over the (3R,4R) enantiomer, or a pharmaceutically acceptable salt, ester or solvate of said compound; and a pharmaceutically acceptable diluent or carrier.

5. The pharmaceutical composition according to claim 4 wherein the active ingredient dexanabinol, or a pharmaceutically acceptable salt, ester or solvate of said compound, has the (3S,4S) configuration and is in enantiomeric excess of at least 99.92% over the (3R,4R) enantiomer.

6. The pharmaceutical composition according to claim 5 wherein the active ingredient dexanabinol, or a pharmaceutically acceptable salt, ester or solvate of said compound, has the (3S,4S) configuration and is in enantiomeric excess of at least 99.95% over the (3R,4R) enantiomer.

8. The pharmaceutical composition according to claim 4 wherein the diluent comprises an aqueous cosolvent solution comprising a pharmaceutically acceptable cosolvent, a micellar solution or emulsion prepared with natural or synthetic ionic or non-ionic surfactants, or a combination of such cosolvent and micellar or emulsion solutions.

9. The pharmaceutical composition according to claim 4 wherein the carrier comprises a solution of ethanol, a surfactant and water.

10. The pharmaceutical composition according to claim 4 wherein the carrier is an

emulsion comprising triglycerides, lecithin, glycerol, an emulsifier, and water.

11. The pharmaceutical composition according to claim 4 comprising a cosolvent solution comprising polyoxyl 35 castor oil and ethanol.

12. The pharmaceutical composition according to claim 11 wherein the polyoxyl 35 castor oil is present in an amount of 30-80% w/w and the ethanol is present in an amount of 20-70% W/W.

13. The pharmaceutical composition according to claim 12 wherein the polyoxyl 35 castor oil is present in an amount of 45-80% w/w and the ethanol is present in an amount of 20-55% W/W.

14. The pharmaceutical composition according to claim 13 wherein the polyoxyl 35 castor oil is present in an amount of 60-80% w/w and the ethanol is present in an amount of 20-40% w/w.

15. The pharmaceutical composition according to claim 11 further comprising a preservative, an antioxidant or a combination thereof.

16. The pharmaceutical composition according to claim 15 wherein the antioxidant is DL-α-tocopherol optionally supplemented with edetic acid.

17. The pharmaceutical composition according to claim 16 comprising 0.1-5% w/w DL-α-tocopherol and 0.001-0.1% w/w edetic acid.

18. The pharmaceutical composition according to claim 4 in unit dosage form.

19. The pharmaceutical composition according to claim 18 suitable for oral administration.

20. The pharmaceutical composition according to claim 18 suitable for parenteral administration.

21. A method for treating neurological disorders, chronic degenerative diseases, CNS poisoning, cognitive impairment, inflammatory diseases or disorders, autoimmune diseases or disorders, pain, emesis, glaucoma and wasting syndromes, by administering to an individual in need thereof a therapeutically effective amount of a pharmaceutical composition comprising as an active ingredient a compound according to claim 1.

22. The method of claim 21 wherein the compound has an enantiomeric excess of at least 99.92% over the (3R,4R) enantiomer.

23. The method of claim 21 wherein the compound has an enantiomeric excess of at least 99.95% over the (3R,4R) enantiomer.

24. The method of claim 23 wherein the compound is administered to an individual to treat a neurological disorder.

Appendix B -- Evidence Appendix

1. **The "Mechoulam Declaration"**
   - By Raphael Mechoulam
   - Filed on March 9, 2005 by the Applicant (acknowledged by the Examiner in the Office Action of April 22, 2005).
2. **The "Yacovan Declaration"**
   - By Avihai Yacovan
   - Filed on September 14, 2005 by the Applicant (acknowledged by the Examiner in the Office Action of December 5, 2005).
3. **The "Bar Declaration"**
   - By Raphael Bar
   - Filed on March 6, 2006 by the Applicant (acknowledged by the Examiner in the Advisory Action of March 16, 2006).

Appendix C -- Related Proceedings Appendix

None